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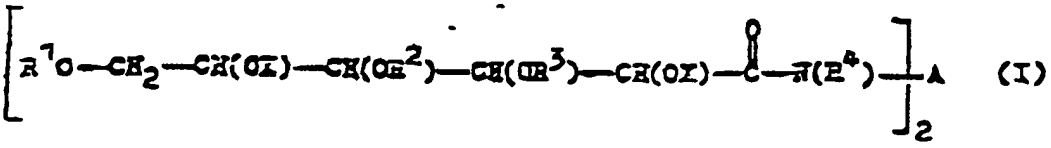
Polysulfuric Acid Esters of Bis-Aldonic Acid Amides and Their Derivates, Process for their Production, and Pharmaceutical

The invention concerns polysulfuric acid esters of bis-aldonic acid amides in which the basic aldonic sulfurs can be glycocydically bonded in positions 3-, 4-, or 6- with a galactopyranosyl, mannopyranosyl, glucopyranosyl, or oligopyranosyl residue. They are therapeutically effective compounds whose production and pharmaceutical composition are also described.

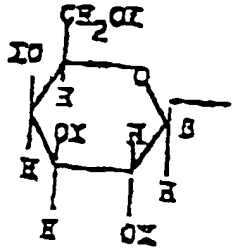
POLYSULFURIC ACID ESTERS OF BIS-ALDONIC ACID AMIDES AND THEIR DERIVATES, PROCESS FOR THEIR PRODUCTION, AND PHARMACEUTICAL

The invention concerns polysulfuric acid esters of bis-aldonic acid amides and their derivates of general formula I,



(I)

wherein either
all the residues R^1, R^2, and R^3 stand for X independently from each other, or
two of the residues R^1, R^2, and R^3 stand for X and the third stands for a residue of formulas II-VII.



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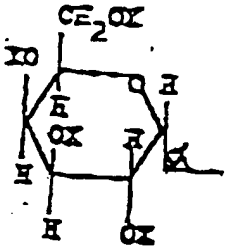

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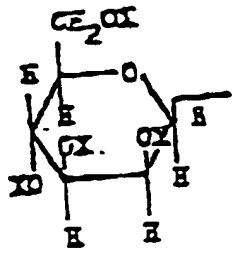

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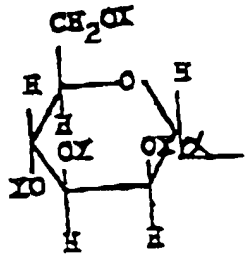

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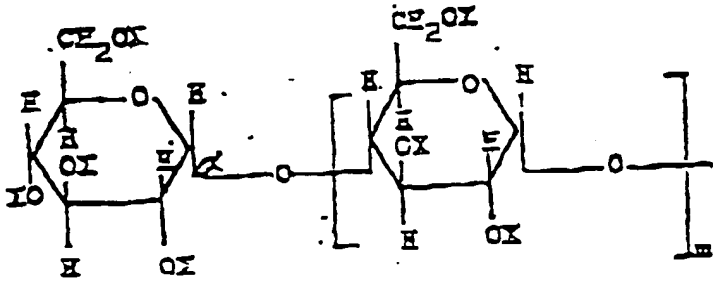
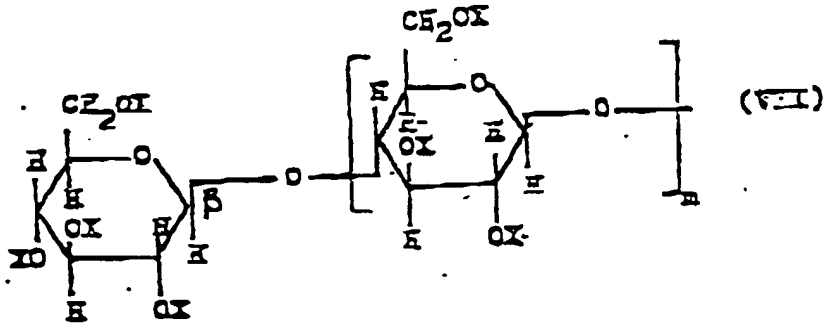
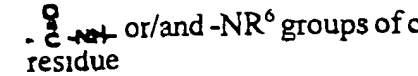


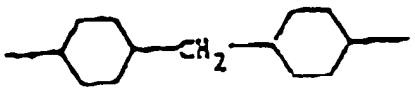
(VI)



(VII)

X means in the formulas I to VII, simultaneously or independently from each other, a hydrogen atom or the group $-SO_2H$, wherein at least one X stands for the group $-SO_2H$,
m stands for 0, 1, 2, 3, 4, 5, or 6,
A in formula I stands for a straight-chain or branched saturated alkyl residue, if necessary substituted with one or several $-CO_2R^5$ residues, with 2 to 22 carbon atoms, and this alkylene residue, if necessary, is interrupted by up to 5 -O-, -S-, -S-S-, $-S(O)_n-$,


or/and $-NR^6$ groups of cycloalkylene or arylene residues, or A stands for a simple bond or the residue

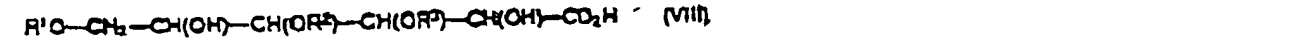


n is 1 or 2,
R^4, R^5, and R^6, simultaneously or independently from each other, mean a hydrogen atom or a C_1—C_{26} alkyl residue,
as well as their salts with inorganic or organic bases.

These compounds according to the invention represent agents with valuable pharmacologic properties, which will be further described below.

For the different substitutes named in connection with the invention and in the description with reference to the residues (in the different cited formulas) are valid the following explanations:

The aldonic acids which are the basis for the polysulfuric acid esters have the general formula VIII



wherein R^1, R^2, and R^3 have the mentioned meaning. These aldonic acids can be available in the D form, the L form, or in the form of racemats, preferably in the form present in nature.

Examples of these aldonic acids comprise the hexanoic acids, allonic acid, altronic acid, galactonic acid, gluconic acid, gulonic acid, idonic acid, mannonic acid, and talonic acid, preferably galactonic acid, gluconic acid, gulonic acid, and mannonic acid. Other examples are derivates of these hexanoic acids which are glycocydically bonded to the oxygen atoms in positions 3-, 4-, or 6- with the residue R^3 or R^2 or R^1 of formulas II to VII, in which X stands for hydrogen. The bond can here be α or β glycocydic. The residues II to V are galactopyranosyl and mannopyranosyl residues. The residues VI and VII are glucopyranosyl residues (for the case that m = 0) and α(1-4) or β(1-4) and bonded oligoglucopyranosyl residues (when m = 1 to 6). Preferably, in the formulas VI and VII, the index m stands for 0 or 1. The saccharide units linked with the aldonic acid are normally available in the D form. Examples of hexanoic acids of general formula VIII, which are substituted with residues of formulas II to VII, are glucopyranosyl gluconic acids, glucopyranosyl mannonic acids, mannopyranosyl mannonic acids, and oligoglucopyranosyl gluconic acids. Preferred are here lactobionic acid (4-O-β-D-galactopyranosyl gluconic acid), gentiobionic acid, melibionic acid (8-O-α-D-glycopyranosyl gluconic acid), mannobionic acid, cellobionic acid (4-O-β-D-glucopyranosylic acid gluconic acid) and maltobionic acid (4-O-α-D-glucopyranosyl gluconic acid) as well as maltotrionic acid and cellotrionic acid.

Examples of salt-bonding bases are trialkylamines with 1 to 6 carbon atoms in the alkyl part such as trimethylamine, triethylamine, tripropylamine, tributylamine, and trihexylamine. Preferred are trimethylamine, triethylamine, and tributylamine.

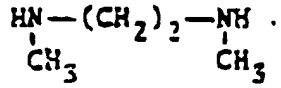
Examples of physiologically tolerated inorganic and organic salts are ammonium, lithium, sodium, potassium, magnesium, calcium, aluminum salts and the salts with ethanolamine, triethanolamine, morpholin, pyridine, and piperidine. Preferred are sodium, potassium, calcium, aluminum, and ethanolamine salts.

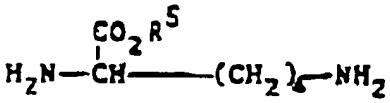
Examples of straight-chain or branched saturated alkyl residues representing A groups with 2 to 22 carbon atoms are ethylene-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, deca-, undeca-, dodeca-, tetradeca-, hexadeca-, octadeca-, icosa-, and decosamethylene as well as methylethylene, methylpropylene, methylbutylene, methylpentylene, and dimethylethylene. Preferred are ethylene-, tri-, tetra-, hexa-, nona-, dodeca-, and docosamethylene and methylpenthylene.

Examples of arylene residues via which the alkyl residues of group A can be interrupted are cyclopenthylene, cyclohexylene, cycloheptylene, and cyclooctylene, wherein here 1,3- and 1,4-cyclohexylene are preferred.

Preferably, the straight-chain or branched saturated alkyl residues of the A group have 2 to 12 carbon atoms. If the straight-chain or branched saturated alkyl residue of group A is interrupted by one of the named residues or groups, they are preferably 1 or 2 such residues or groups.

Special examples of the defined alkyl residues representing group A are the following groups derived from α,β diamines:

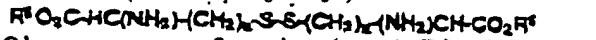




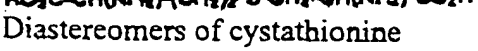
Enantiomers of lysin (R^5 = H) and their esters (H^9 = C_1-C_6 alkyl)

with S-atoms:

Diestereomers of lanthionin (R^3 = H)
and ester (R^5 = C_1-C_6 alkyl)



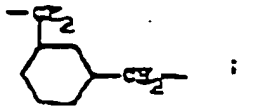
Olastereomers of cystine (x = 1, R^3 = M)
and ester (R^5 = C_1-C_6 alkyl)
Diastereomers of homocystine (x = 2, R^5 = H)
and ester (R^5 = C_1-C_6 alkyl)



Diastereomers of cystathionine

with NH groups:	
$H_2N(-CH_2-CH_2-NH)_x-CH_2-CH_2-NH_2$ $H_2N-(CH_2)_2-NH-(CH_2)_2-NH-(CH_2)_2-NH_2$ $H_2N-(CH_2)_3-NH-(CH_2)_2-NH-(CH_2)_3-NH_2$ $H_2N-(CH_2)_6-NH-(CH_2)_6-NH_2$ $H_2N-(CH_2)_3-NH-(CH_2)_4-NH-(CH_2)_3-NH_2$ $H_2N-(CH_2)_4-NH-(CH_2)_3-NH_2$ $H_2N-(CH_2)_3-NH-(CH_2)_2-NH-(CH_2)_3-NH_2$	x = 1 diethylenetriamine x = 2 triethyleneteramine x = 3 tetraethylenepentamine 1,9-diamino-3,7-diazanonane 1,10-diamino-4,7-diazadecane bis-(6-aminohexyl)amine spermine spermidine 1,11-diamino-4,6-diazaundecane
with O atoms:	
$H_2N-(CH_2)_2-O-(CH_2)_2-NH_2$	bis-(2-aminoethyl)ether

Preferably, the A group can stand for the following residues:



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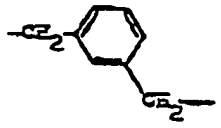

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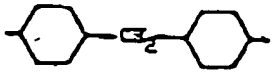
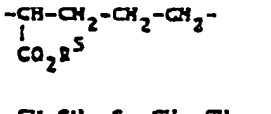
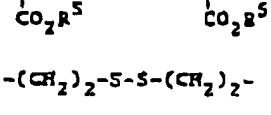
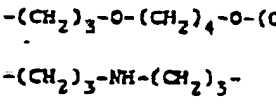
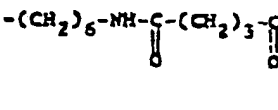






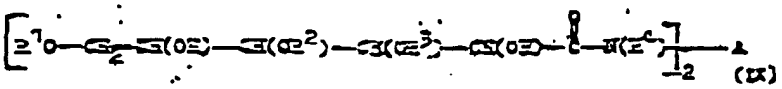


with p = 1 or 2

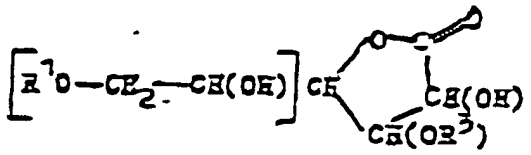


Examples of C_1-C_6 alkyl residues of the groups R^4, R^5, and R^6 are methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, tert.-butyl, neopentyl, wherein methyl, ethyl, n-propyl, isopropyl, tert.-butyl, and n-butyl are preferred.

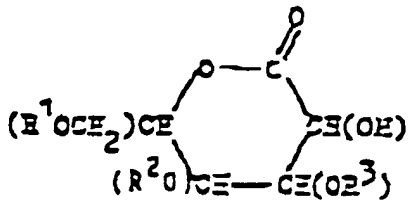
The invention concerns a process for producing polysulfuric acid esters of bis-aldonic acid amides of general formula I, which are characterized in that bis-aldonic acid amides of general formula IX



wherein R^1, R^2, R^3, R^4, and A are the mentioned meanings, wherein however X in the formulas II to VII stands for hydrogen mixed in an aprotic solvent with a sulfatizing agent and the products obtained in this way are transferred with an inorganic or organic base into the corresponding salts. One obtains the compound of general formula IX similar as in the already known process (for example: F. Scholnick, P.E., Pfeffer, J. Dairy Sci. 83 (3), 471 (1980); W.N. Emmerling, B. Pfannenmueller, Starch 33 (6), 202 (1981)). For producing the bis-aldonic acid amides of general formula IX, lactones of the lactic acids of general formula VIII are allowed to react in a solvent with a diamino compound R^4-HN-A-NHR^4. The lactones can thereby also be used in the 1,4-lactone form of general formula X as well as in the 1,5-lactone form of general formula XI.



(X)



(XI)

One obtains the compounds of general formulas X and XI by water separation of the aldonic acids VIII. The aldonic acids can, according to processes known from the literature (for example, W.N. Emmerling, B. Pfannenmueller, Starch, 33 (6), 202 (1981); R. Schaeffer, H.S. Isbell, J. Am. Chem. Soc. 81, 2178 (1959); H.W. Diehl et al, Carbohydrate Research 38, 384 (1974)) be obtained by electrochemical or hypohalogenic oxidation of the corresponding aldones. For the production of bis-aldonic acid amides of general formula IX, per mol diamine compound are added 2 mol aldonic acid lactone. Suitable solvents for the transformation are methanol, ethanol, ethylenegylcol, dimethylsulfoxide, dimethylformamide, or N-methylpyrrolidone. Preferred is dimethylformamide. The reaction times amount from several hours to days, preferably between 5 and 8 hours. The reaction temperatures lie between room temperature and the boiling temperature of the each solvent, preferably between 40°C and 80°C. The aldonic acid amides crystallize either from the reaction solution or they can be precipitated by adding an organic solvent. Suitable therefor are methanol, ethanol, isopropanol, or acetone, preferably isopropanol.

The bis-aldonic acid amides of general formula IX are the object of German patent application P..... of the same applicant and with the same filing date (Case BAA, entitled "Bis-aldonic Acid Amides and Process for their Production"), whose disclosure should be included herein by reference.

For the production of these compounds of general formula I, the bis-aldonic acid amides of formula IX are dissolved or suspended in an aprotic solvent. Suitable are pyridine, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, etc., preferably dimethylformamide.

The mixture is heated to temperatures between 20°C and 100°C, preferably between 30°C and 70°C, and a sulfatizing agent is added. Examples thereof are chlorosulfonic acid, sulfuric trioxide, oleum, ether- and amine sulfuric oxide complexes. Preferred are the sulfuric trioxide complexes with trimethylamine, triethylamine, and pyridine.

To obtain polysulfuric acid esters from bis-aldonic acid amides of general formula I, wherein each X stands for the group $-SO_2H$ are added for each esterizable hydroxyl group 1 to 2 equivalent sulfatizing agents, preferably 1,4 - 1,7 equivalents. Compounds in which each X does not stand for the $-SO_2H$ group is are obtained when the sulfatizing agents are added in excess. Depending on how high the sulfur content of the product should be, the quantity of sulfatizing agent is selected. Preferably used are quantities between 0.5 and 1 equivalent sulfatizing agent per esterizable hydroxyl group. The reaction mixture is stirred 1 to 24 hours at temperatures between 20°C and 100°C. From the polysulfate compounds obtained in this manner of general formula I, wherein X stands for $-SO_3H$, which can also be present in the form of salts of amines of the used amine-sulfuric trioxide complexes, one obtains the corresponding salts of inorganic bases by adding to these bases or their inorganic salts. Preferably used here are the hydroxides and acetones of alkali and earth metals. Salts of physiologically harmless organic bases are obtained by using a sulfur trioxide complex of these bases in the sulfatizing reaction or by treating the earth alkali or alkali salts with a cationic exchanger in the sour form and then neutralizing the acid sulfuric acid half-ester with the organic base. The isolation of the compounds according to the invention takes place in general by precipitation from the reaction solutions or from aqueous solutions with organic solvents. Suitable organic solvents are methanol, ethanol, isopropanol, or acetone, preferably methanol.

The compounds can be purified by repeated precipitation from aqueous solutions with the above-named solvents and by treating with active carbon or hydrogen peroxide. In general, the products obtained in this way are mixtures with a more or less high content of compounds, whose hydroxyl groups are esterized with sulfate residues and compounds whose hydroxyl groups are only rarely sulfatized, depending upon the quantity of used sulfatizing agent. The obtained mixtures can be separated, if necessary, by different separation processes into products with a single structure of sulfate residues. The separation can occur via different physical separation processes such as, for example, fractioned filling, gel-ion exchange, or affinity chromatography, HPLC, or electrophoretic processes. Preferably is the fractioned filling. For example, an aqueous solution of the product mixture is produced and mixed with the single or multiple quantity of organic solvent. Suitable are solvents that mix with water such as methanol, ethanol, isopropanol, acetone, or tetrahydrofurane, preferred is methanol. The precipitation obtained in this manner can be reduced. In general, the compounds with higher sulfate content are enriched in the precipitation, those with lower sulfate content are enriched in the remaining solution. By repeated fractioned precipitation of the precipitate or residues are obtained compounds with a defined number of sulfate groups.

In a preferred embodiment of the process according to the invention, the compounds of formula I of the aldonic acids of formula VIII are produced without isolation of the necessary intermediate steps.

Herein, via the commercially known processes or the processes known from the literature (for example, W.N. Emmerling, B. Pfannenmueller, Starch 33 (6), 202 (1981); R. Schaffer, H.S. Isabell, J. Am. Chem. Soc. 81, 2178 (1959), H.W. Diehl et al, Carbohydrate Research 38, 384 (1974))), synthesized alkali or earth alkali salts of aldonic acids VIII are produced by means of a cationic exchanger in an aqueous solution of free aldonic acids VIII and the same is narrowed down to a large extent. The lactones corresponding to the aldonic acids VIII are produced now on site by water separation. For this purpose, the residue that generally represents a water-containing mixture of aldonic acid and lactone is dissolved in a high boiling solvent. Examples for high boiling solvents are dimethylsulfoxide, dimethylformamide, N-methylpyrrolidone, dimethoxymethylether, etc., preferably dimethylformamide. Now, a second low boiling solvent is added, which can form an azeotrope with water. Suitable solvents are, for example, n-pentane, n-hexane, cyclohexane, benzol, etc., preferred is n-hexane. At the moisture separator, water is quantitatively separated from the aldonic acids. Then, the low boiling drag agent is

distilled and the lactone remaining in the high boiling solvent is transformed without isolation of the same with the diamine compound. The reaction temperatures lie therein between 20°C and 120°C, preferably between 50°C and 60°C. It is stirred over time periods of 3 to 24 hours, preferably 3 to 8 hours. Without isolation of the produced bis-aldonic acid amide, the same is brought into a reaction with a sulfatizing agent in the same container. The reaction conditions as well as isolation and purification of the product are described in the previously-cited process.

The compounds of general formula I represent pharmacologically valuable substances. They possess antithrombotic and antiinflammatory properties. The compounds according to the invention are therefore suitable for treatment of rheumatic cycle as well as the prophylaxis and therapy of venous and arterial thromboses. The object of the invention is therefore also a pharmaceutical for application in humans and animals. Preferred is its use in humans.

Particularly surprising is the antithrombotic effectiveness of the compounds according to the invention.

Until now, for the treatment of thrombosis prophylaxis, mainly heparin was utilized. Heparin is a mucopolysaccharide that is isolated from animal tissue, in particular pig intestines (Thomas, D.P. (1981) in Clinics in Hematology, Vol. 10, pp. 443-458, Saunders Comp. Ltd. 1981). Aside from heparin, also other naturally occurring mucopolysaccharides such as dermatan sulfate or heparan sulfate have antithrombotic properties (Rosenberg, R.D., Rosenberg, J.S. (1984), J. Clin. Invest. 74, 1-8; Sie, P., Ofosu, F., Fernandez, F., Buchanau, M.R., Pathou, M., Boneu, B. (1986) Br. J. Hematol. 84, 707-714). A semisynthetic chondrolithin polysulfate is also known, for example, from German patent publication 3,118,568, which among others has antithrombotic properties. Only heparin is, however, used therapeutically. In earlier times, some low molecular heparines were developed for clinical applications. These were substances which were obtained by different chemical or enzymatic depolymerization processes from heparin (Thomas, D.P., Merton, R.E. (1982) Thrombos. Res. 28, 343-350; Walenga, J.M., Fareed, J. Pathou, M., Samana, M., Lormeau, J.C., Chosy, J. (1986) Thrombos. Res. 43, 342-248; Koller, M., Schoh, U., Buchmann, P., Larginder, F., von Felten, A., Frick, P.G. (1986) Thrombos. Hemostas. 38, 242-246).

A disadvantage of heparin and low molecular heparin is based on that they are naturally originated (for example, originating from animals). From the animal tissue originate therefore small quantities of antigen, which can lead to anaphylactic reactions such as a decrease of thrombozylene, thrombosis, and embolia. These side effects are relatively rare, but still serious and clinically hard to control.

Instead, the compounds according to the invention are fully synthetic and therefore free of animal antigens.

Another essential common complication in thrombosis prophylaxis with heparin and low molecular heparin is the occurrence of hemorrhage. Substances which cause less hemorraghe with the same antithrombotic effect can therefore represent an essential therapeutic progress.

For testing the compounds according to the invention as to their antithrombotic effectiveness and antiinflammatory effectiveness were used several pharmacologic tests.

1. Acceleration of the Fibrinolysis

The occurrence of a clinically manifest (greater) thrombus can be prevented in different ways. On the one hand, the factors which are participant in the formation of the primary thrombus, such as the blood platelet aggregation or blood coagulation system, are deactivated. On the other hand, the dissolving of the primary thrombus can be accelerated by reinforcing the body fibrinolysis. A reinforcement of the body fibrinolysis can also serve to dissolve the already clinically manifest thrombi. The fibrinolytic effect of a substance has great importance therefore in the prophylaxis and therapy of thromboses. The fibrinolytic effect of the substances according to the invention was determined in the following test. The test is an easy modification of a method known from the literature for determining the fibrinolytic effect (Kluft., C. (1979) Thromb. Hemostas. 41, 365-383).

Fibrinolysis Test

The fibrinolysis was determined by means of plasminogen-containing fibrin plates.

Petri bowls, ⌀ 9 cm, were preheated to 40°C. By swinging the bowl were obtained 3 ml of a 2% solution of fibrinogen (Behringerwerke, Marburg) in water. 1 ml of a plasminogenic solution, 2 CTA/ml (Behringerwerke, Marburg), 3 ml of a 1% agarose solution (Serva, Heidelberg) in 50 mM TAIS/HCl, pH 7.8, and 1 ml of a solution of 15 U/ml thrombin (Behringerwerke, Marburg) were pipetted in water. After cooling of the plate, holes with a 5 mm diameter were punched.

0.1 ml plasma (Human Standard Plasma, Behringerwerke, Marburg), 0.8 ml water, and 0.1 ml solution of the test substance in different concentrations were incubated for 10 minutes at 37°C. After adding 0.9 ml 0.025% acetic acid it was incubated for 5 minutes at 4°C and then centrifuged at 2000 g for 5 minutes. The precipitation was received in 0.1 ml buffer (20 mM TRIS/HCl, 100 mM NaCl, 2.7 mM EDTA, pH 7.8).

0.02 ml of this solution and 0.065 ml 14.3 mM flutenantinic acid solution (Sigma, Taufkirchen) in buffer were pipetted into the application holes of the fibrin plates. After 24 hours at 37°C, the lysis holes were planimetered. The surface of the lysis hole with respect to the lysis surface without substance addition served as measure for the fibrinolysis-increasing activity.

Result: the results are shown in the following table.

Substance of Example	Fibrinolysis at 2 ug/ml (mm^3)
23	21.6
20	19.2
24	17.8
Heparin	14.8

2. Inhibition of Blood Coagulation

The inhibition of the blood coagulation can be easily measured in a simple manner by means of the activated partial thromboplastic cell aPTT. It provides an insight into general inhibition of the activated coagulation system. To reduce the occurrence of a hemorraghe, an inhibition of the blood coagulation system which is as low as possible is desired.

Coagulation Test, aPTT

0.1 ml plasma and 0.1 ml Fathromtin® (Behringerwerke, Marburg) were incubated for 2 minutes at 37°C and were mixed with 0.1 ml of 25 mM $CaCl_2$ solution. The coagulation time is measured in a Schnitger & Gross coagulatometer. The agent is formed per concentration from 6 individual determinations. As standard serves a heparin of the Pharmindustrie company with 175 E/mg.

The extension of the coagulation time is transformed via a calibration curve in heparin units. Since the calibration curves are not parallel, the extension of the coagulation time of 150% of the initial value is selected as reference point.

Result: the following table shows the heparin units of compounds according to the invention.

Substance of Example	E/mg
23	30.9
25	5.85
20	42.1
24	14.1
31	10.2
34	15.1
Heparin	175
Fragmin (low mol. heparin)	84.6

3. Influencing of the Coagulation Time

A 2 mm long piece of the tail of rats was cut. The time until the end of the bleeding was measured. The animals were administered the tested substance 5 minutes after the end of the bleeding in different concentrations or physiologic cooking salt solutions (control). Groups of 20 animals each were treated. The extension of the coagulation time with respect to the control is expressed in percentages.

Substance of Example	Extension of the Coagulation Time (%)		
	Dosis (mg/Kg)		
	0.25	0.5	2
20	-	5.1	35.1
Heparin	55.4	120	

4. Antiinflammatory Effect

In inflammatory processes, large quantities of reactive oxygen species were released by the phagocytes (polymorph-core leucocytes and macrophages), among those superoxide radicals and hydroxyl radicals. These radicals are participants in the tissue destruction which inhibit the radical formation in leucocytes, are therefore of great therapeutic interest in the fight against inflammations (Fiche, L., Glartz, H., Backmann, R. (1985) in The Pharmacology of Inflammation, Vol. 6 (Bonta, I. et al eds.) pp. 255-291, Bisevier, Amsterdam-New York.

The radical formation of leucocytes can be measured by measuring the luminol-reinforced chemical luminescence in the blood (Peter, M. et al (1985) in Chi. Forum 85 (Stalzner, F., eds.), pp. 51-84, Springer Publishers, Berlin).

Test as to Antiinflammatory Effects

The test substances are dissolved in PBS and dilution series in PBS are assigned. Into cuvettes, which fit a 1251 luminometer of LKB, are pipetted 600 µl PBS, 100 µl solution of the test substance, 100 µl zymosan suspension (100 mg/ml) and 100 µl rabbit citrate blood. The measurement is started with 100 µl 10^{-3} M luminol solution. The chemical luminescence is measured over 90 minutes every 5 minutes in

each formulation. The maximum chemical luminescence is determined. As reference value serves a formulation without testing substance. As empty value serves a formulation without zymosan addition. Per substance are carried out three independent determinations. The calculation of the remaining chemical luminescence takes place according to formula:

$$\frac{CL_{max}\ (Subst) - CL_{max}\ (Leer)}{CL_{max}\ (Ref) - CL_{max}\ (Leer)} \times 100$$

From a semilogarithmic entry of the residual chemical luminescence in a log concentration result concentrations of 50% Cl inhibition (IC_{14} values).

Results

The inhibition of the luminol-reinforced Cl by means of the compounds according to the invention is shown in the following table.

Substance of Example	IC_{14} (µg/ml)
23	225
25	155
20	540
24	220
31	170
Indomethacin	240

The object of the invention are also pharmaceutical preparations which, aside from non-toxic inert pharmaceutically suitable carrier substances contain also one or several active substances according to the invention or consist of one or several active substances according to the invention.

Under non-ionic inert pharmaceutically suitable carrier substances are to be understood solid, semisolid, or liquid thinners, fillers, and formulation auxiliary substances of any kind.

As preferred pharmaceutical preparations can be used tablets, dragees, capsules, pills, granulates, suppositories, solutions, suspensions, and emulsions, pastes, ointments, gels, cremes, lotions, powders, sprays, and aerosols.

Tablets, dragees, capsules, pills, and granulates can contain the active substance or substances aside from the usual carrier substances such as a) filler and stretching substances, for example starches, lactose, sugar cane, glucose, manit, and silica acid; b) bonding agents, for example carboxylmethylcellulose, alginates, gelatins, polyvinylpyrrolidone; c) moisture prevention means, for example glycerin; d) dispersion means, for example agar-agar, calcium carbonate, and sodium bicarbonate; e) solution delayers, for example paraffin; and i) resorption accelerator; g) wetting agents, for example getyl alcohol, glycerin monoestearate; h) adsorption means, for example kaolin and bentonit; and l) lubricants, for example talcum, calcium-, and magnesium stearate and solid polyethylene glycols or mixtures of the substances listed under a) to i).

The tablets, dragees, capsules, pills, and granulates can be provided with the usual coatings, if necessary containing opalization means, for example, sugar, coating material, and also can be so structured that they release the active substance or substances preferably at a specific part of the intestinal tract, if necessary with a delayed effect, wherein as imbedding masses can be used, for example, polymer substances and wax.

The active substance or substances can be available, if necessary, with one or several of the above-mentioned carrier substances also in microencapsulated form.

The suppositories can contain, aside from the active substance or substances, the usual water-soluble or water-insoluble carrier substances, for example, polyethylene glycols, fats, for example cocoa fat, and higher esters (for example, C_{14} alcohol with C_{16} fatty acid or mixtures of these substances).

Ointments, pastes, cremes, and gels can contain, aside from the active substances, the usual carrier substances, for example, animal and vegetable fats and their derivates, wax, paraffin, emulgators, starches, traganth, cellulose derivates, polyacrylates, polyethylene glycols, silicones, bentonites, talcum, silica acid, and zinc oxide or mixtures of these substances.

The sprays and powder can contain, aside from the active substance or substances, the usual carrier substances, for example, lactose, talcum, silica acid, aluminum hydroxide, calcium silicate, and polyamide powder or mixtures of these substances. The sprays can also contain the usual propellants, for example, chlorofluor hydrocarbon.

The solutions and emulsions can contain, aside from the active substance or substances, the usual carrier substances such as solvents, solution promoters, and emulgators, for example, water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils, in particular cottonseed oil, peanut oil, cashew nut oil, corn seed oil, olive oil, ricinus oil, and sesame seed oil, glycerin, glycerin formate, polyethylene gycols and fatty acid esters of sorbitans or mixtures of these substances.

For parenteral application, the solutions and emulsions can also be sterilized and be available in blood-isotonic form.

The suspensions can contain, aside from the active substance or substances, the usual carrier substances such as liquid thinners, for example, ethyl alcohol, propylene alcohol, suspension means, for example, ethoxylated isosteryl alcohol, polyoxyethylene sorbit- and sorbitan ester, microcrystalline cellulose, aluminum metahydroxide, bentonit, agar-agar, or traganth or mixtures of these substances.

The named formulation forms can also contain dyes, preservatives, as well as aroma and taste improving additives, for example, peppermint and eucalyptus oil, and sweeteners, for example, saccharin.

The therapeutically effective compounds should preferably be available in the above listed pharmaceutical preparations, preferably in a concentration of approximately 0.1 to 99.5, preferably of approximately 0.5 to 95 mass-% of the total mixture.

The above-listed pharmaceutical preparations can contain, aside from the active substances according to the invention, also other pharmaceutically active substances.

The production of the above-listed pharmaceutical preparations takes place in the usual way according to known methods, for example, by mixing of the active substances with the carrier substances.

To this invention belongs also the application of the active substances as well as the pharmaceutical preparations, which contain one or several active substances, in human and veterinary medicine for preventing, improving, and/or healing the above-listed diseases.

The active substances or the pharmaceutical preparations can be applied locally, parenterally, rectally, and/or as aerosol, preferably parenterally.

In general, it has been shown to be advantageous to administer the active substance or substances in total quantities of approximately 0.1 to approximately 100, preferably 0.5 to 50 mg/Kg body weight every 24 hours, if necessary in the form of several individual doses for obtaining the desired results.

However, it may be necessary to deviate from these named dosages, in particular in dependence upon the type and the body weight of the subject to be treated, the type and the seriousness of the disease, the type of preparation, and the application of the pharmaceutical as well as the time duration or interval within which the administration takes place. In this way, it can be sufficient in some cases to make do with

less of the above-named active substances, while in other cases the above-listed quantities of active substance may have to exceeded.

The following examples explain the invention more closely but should not limit its scope in any way.

Example 1

N,N-1,3-Propandylbis-O-Gluconamide

7.13 g D(+) gluconic acid-1,5-lactone are dissolved in 40 ml dimethylformamide and are mixed with 1.67 ml 1,3-diaminopropane. This is then heated to 80°C and stirred for 5 hours. The obtained precipitation is filtered, washed with methanol, and dried. 7.88 g of a white powder are obtained.

Melting point:	165 - 173 °C
IR (KBr):	ν = 3540, 2960, 2915, 2890, 1660, 1537, 1100, 1040 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,76 (dt,2H, 6,5Hz); 3,30 (t, 4H, 6,5Hz); 3,4 - 4,0 (m, 8H); 4,09 (m, 2H); 4,30 (d, 2H, 3Hz); 4,70 (H_2O, LSL)

Example 2

N,N-1,12-Dodecandylbis-D-Gluconamide

7.1 g D-gluconic acid-1,5-lactone are suspended in 90 ml dimethylformamide, are mixed with 4.0 g 1,12-diaminododecane, and the mixture is stirred for 5 hours at 60°C. After cooling, the mixture is stirred in 0.5 l methanol, the fatty substance is collected and washed in methanol. Now the solids are suspended in 1 N HCl, stirred for one hour at room temperature, the fatty substance is again collected and washed with water, acetone, and finally with diethylether. 9.9 g of a white powder are obtained.

Melting point:	192 - 196 °C
IR (KBr):	ν = 2920, 2850, 1630, 1550, 1085, 1027 cm^{-1}
^{1}H-NMR (DMSO - d_6):	δ 0,7 - 1,8 (m, 20H); 3,08 (m, 4H); 3,25 - 3,75 (m,8H); 3,75 - 4,2 (m, 4H); 4,40 (S, 10H); 7,51 (t, 2H, 6,5Hz); L SL: Tetramethylsilan

Example 3

N-N'-1,3-Propandylbis(4-O-β-O-Galactopyrenosyl-D-Gluconamide

395.4 g calcium lactobionate are dissolved in 1.2 l water and the solution is treated for 1 hour with 0.7 l Lewatit S 100 (H form) in a batch process. The exchanger is suctioned off and washed with 2 x 1 l water. The unified eluate is suctioned in a vacuum. Now, the glass-like residue is dissolved in 800 ml amine-free dimethyl formamide, 800 ml n-hexane are added and, under strong stirring, the water separator is brought to boiling. After the water separation has concluded, the n-hexane is distilled, mixed with 43 ml 1,3-diaminopropane and stirred for 7 hours at 63°C. Now the mixture is stirred in 6 l isopropanol, the solids are collected and washed with 1 l isopropanol. After separation are obtained 360 g of other fully solid substances. For purifying, the same is dissolved in 2 l water. The solution is treated for 1 hour with

100 ml Lewatit S 100 (H form), then with 100 ml amber lysate A 21 (OH form). After freeze-drying is obtained the compounds of the title in its pure form.

Melting point:	125 - 132 °C
IR (KBr):	ν = 2930, 1645, 1650, 1080 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,75 (dt,2H, 6Hz); 3,27 (t, 4H, 6Hz); 3,4 - 4,1 (m, 20H); 4,15 (t, 2H, 3Hz); 4,39 (d, 2H, 3Hz); 4,54 (d, 2H, 7Hz); 4,70 (H_2O, i.St.)
^{13}C-NMR (D_2O):	δ 30,78; 38,99; 83,73; 84,85; 71,30; 73,12; 73,74; 74,14; 74,50; 75,08; 75,18; 77,99; 83,71, 108,10; 178,84 i. St.: CH_2OH δ 51,58

Example 4

N-N'-1,8-Hexandylbis(4-O-β-D-Galactopyranosyl-D-Glyconamide

17.0 g lactobionic acid-1,6-lactone are suspended in 100 ml amine-free dimethylformamide, mixed with 2.3 g 1,6-diamine volume, and stirred for 6 hours at 80°C. After cooling, it is filtered and the filtrate is stirred in 1 l diethylether. The partially oily precipitation is dissolved in 60 ml water and treated with 80 ml ionic exchanger (Merck 4765, H form). It is filtered and, after lyophilization, 10.5 g colorless powder are obtained, which takes on a brown color when exposed to 175°C.

IR:	ν = 2930, 2880, 1645, 1648, 1080 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,0 - 1,8 (m, 8H); 3,25 (t, 4H, 5,5Hz); 3,3 - 4,1 (m, 20H); 4,15 (t, 2H, 3Hz); 4,38 (d, 2H, 3Hz); 4,55 (d, 2H, 7Hz); 4,70 (H_2O) i. St.: 3-Trimethylsilyl-propansulfonsäure-Na-Salz
^{13}C-NMR (D_2O):	δ 28,19; 30,69; 41,53; 63,88; 84,84; 71,25; 73,08; 73,72; 74,12; 74,96; 75,18; 77,97; 83,81; 108,08; 178,48 i. St.: CH_2OH δ 51,54

Example 5

N,N'-1,12-Dodecandylbis(4-O-β-D-Galactopyranosyl-D-Gluconamide

40.8 g lactobionic acid-1,5-lactone are suspended in 150 ml amine-free dimethylformamide, 12.0 g 1,12-diaminododecane are added and stirred for 8 hours at 80°C. While stirring, the mixture is dripped into 1.5 l isopropanol. The precipitation is washed with isopropanol and dissolved in 250 ml water. The solution is treated first with 20 ml of an acid ion exchanger (Lewatit S 100), then with a base ion exchanger (Merck 4787). After lyophilization are obtained 35.0 g of a colorless powder. Melting point: 79-81°C.

IR:	ν = 2920, 2850, 1645, 1550, 1080 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,8 - 1,9 (m, 20H); 3,24 (t, 4H, 5,5Hz); 3,4 - 4,1 (m, 20H); 4,17 (t, 2H, 3Hz); 4,38 (d, 2H, 3Hz); 4,55 (d, 2H, 7Hz); 4,68 (H_2O, i. St.)
^{13}C-NMR (D_2O):	δ 29,02; 31,38; 31,70; 41,88; 63,64; 64,69; 71,20; 73,08; 73,72; 74,17; 75,03; 75,20; 77,97; 83,72; 108,12; 178,24; i.St. CH_2OHδ51,56

Example 6

N,N'-1,5-Nonadylbis(4-O-β-D-Galactopyranosyl-O-Glyconamide

Production and purification similar to Example 5. From 15.0 g lactobionic acid and 3.47 g 1,9-diaminononane are obtained 15.0 g of the compound of the title:

IR	ν = 2930, 2860, 1660, 1545, 1080 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,9 - 1,8 (m, 14H); 3,20 (t, 4H, 8,5Hz); 3,3 - 4,1 (m, 20H); 4,15 (t, 2H, 3Hz); 4,38 (d, 2H, 3Hz); 4,55 (d, 7Hz); 4,68 (H_2O, l.St.)

Example 7

N-N'-1,12-Dodecandylbis(4-O-β-D-Glucopyrnosyl-D-Gluconamide

2.04 g cellobionic acid-1,5-lactone (H.W. Diehl et al, Carbohydr. Res. 38, 384 (1974) are transformed similar to Example 6 with 0.80 g 1,12-diaminododecane and 0.80 g of the compound of the title are obtained.

IR:	ν = 2925, 2860, 1645, 1545, 1075, 1040 cm^{-1}
^{1}H-NMR (D_2O):	δ 0.7 - 1,8 (m, 20H); 3,0 - 4,8 (m, 30H); 4,68 (H_2O, l.St.)

Example 8

N,N'-1,12-dodecandylbis(4-O-β-O-Glucopyranosyl-D-Gluconamide

20.0 g calcium maltobionate (W.N. Emmerling, B. Pfannenmueller, Starch 33. 202 (1981)) similar to Example 3 with 1,12-diaminododecane and 17.8 g product are obtained.

IR:	ν = 2925, 2860, 1650, 1545, 1145, 1075, 1030 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,7 - 1,9 (m, 20H); 3,20 (t, 4H, 5,5Hz); 3,3 - 4,4 (m, 24H); 5,15 (d, 2H, 3Hz); 4,68 (H_2O, l.St.)

Example 9

N,N'-1,12-dodecandylbis(6-O-α-O-Galactopyranosyl-O-Gluconamide

3.98 g potassium maltobionate (Sigma-Chemie) are transformed similar to Example 3 with 1.00 g 1,12-diaminododecane and 3.3 g of the compound of the title are obtained.

Melting point:	114 - 121 °C
IR (KBr):	ν = 2925, 1654, 1645, 1560, 1150, 1080, 1030, 980 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,8 - 1,8 (m, 20H); 3,20 (m, 4H); 3,4 - 4,2 (m, 22H), 4,29 (d, 2H, 3Hz); 4,95 (s, 2H); 4,68 (H_2O, l. St.)

Example 10

N,N'-1,3-Propandylbis(6-O-α-D-Galactopyranosyl-O-Gluconamide

Production similar to Example 9. From 3.98 g potassium maltobionate and 0.37 g 1,3-diaminopropane are obtained 3.0 g product.

Melting point: IR (KBr): ^{1}H-NMR (D_2O): ^{13}C-NMR (D_2O):	90 - 95 °C ν = 2925, 1645, 1550, 1152, 1080, 1030, 975 cm^{-1} δ 1,76 (m, 2H, 6,5Hz); 3,30 (t, 4H, 6,5 Hz); 3,4 - 4,2 (m, 22H); 4,33 (d, 2H, 3Hz); 4,96 (s, 2H); 4,70 (H_2O, L St.) δ 30,73; 38,96; 63,75; 70,94; 74,13; 71,90; 72,12; 73,06; 73,52; 74,52; 75,97; 100,99; 178,91

Example 11

N,N'-α,α'-m-Xylodylbis(4-O-β-O-Galactopyranosyl-O-Gluconamide

If in a process according to Example 5 are used 17.0 g lactobionic acid-1,5-lactone and 3,3 ml 3-(aminomethyl)-benzylamine, in the same way are obtained 12.2 g of the compound of the title as a colorless powder.

IR: ^{1}H-NMR (D_2O):	ν = 2920, 1685, 1545, 1080 cm^{-1} δ 3,3 - 4,6 (m, 30H); 4,68 (H_2O); 7,24 (m, 4H)

Example 12

N,N'-4,4'-m-Dicyclohexylmethandylbis(4-O-β-D-Galactopyranosyl-D-Gluconamide

Production and purification similar to Example 5 with 17.0 g lactobionic acid-1,5-lactone and 5.3 g 4,4'-diamino-dicyclohexylmethane. Yield: 21.3 g.

IR: ^{1}H-NMR (D_2O):	ν = 2930, 2850, 1645, 1545, 1080 cm^{-1} δ 0,6 - 2,2 (m, 20H); 3,2 - 4,6 (m, 28H), 4,68 (H_2O)

Example 13

N,N'-1,8-(3,4-Dithiahexandylbis)4-O-β-D-Galactopyranosyl-O-Gluconamide

17.0 g lactobionic acid-1,5-lactone and 3.63 g cystamine dihydrochloride are added to 50 ml amine-free DMF at room temperature with 6.9 ml triethylamine and stirred additionally for 8 hours at 80°C. It is precipitated with 500 ml ethanol and the precipitate is again treated as in Example 5. 13.2 g of a white powder are obtained.

IR:	ν = 2925, 1650, 1545, 1080 cm^{-1}
^{1}H-NMR (D_2O):	δ 2.90 (t, 4H, 6Hz); 3.2 - 4.1 (m, 24H); 4.18 (t, 2H, 3Hz); 4.38 (d, 2H, 3Hz); 4.55 (d, 2H, 7 Hz); 4.68 (H_2O, i. St.)

Example 14

N,N'-1,7-(4-Azaheptandylbis)4-O-β-D-Galactopyranosyl-D-Gluconamide

17.0 g lactobionic acid-1,5-lactone are suspended in 100 ml amine-free dimethylformamide, transferred at room temperature with 2.28 ml bis-(3-aminopropyl)-amine and stirred for 10 hours. Then, they are stirred for 4 hours at 40°C and filtered. The filtrate is stirred into 900 ml acetone and, after washing with acetone and drying, are obtained 23.0 g white crystals. These are dissolved in 60 ml water and precipitated with 800 ml acetone. The partially oily precipitate is dissolved in 150 ml water, filtered, and lyophilized. Yield: 18.5 g.

IR:	ν = 2920, 1650, 1545, 1080 cm^{-1}
^{1}H-NMR (D_2O):	δ 1.82 (dt, 4H, 6Hz); 2.91 (t, 4H, 6Hz); 3.30 (t, 4H, 6Hz); 3.45 - 4.6 (m, 28H); 4.68 (H_2O)

Example 15

N,N'-1,12-(4,3-Oloxadodecandylbis)4-O-β-O-Galactopyranosyl-O-Gluconamide

Production and purification according to Example 5. From 17.0 g lactobionic acid-1,5-lactone and 6.1 g 1,12-diamino-4,9-dioxa-dodecane are obtained 18.9 g of the compound of the title.

^{1}H-NMR:	δ 1.4 - 2.0 (m, 8H); 3.1 - 4.1 (m, 32H); 4.6 (t, 2H, 3Hz); 4.38 (d, 2H, 3Hz); 4.55 (d, 2H, 7Hz)

Example 16

N,N'-Dimethyl-N,N'-1,2-Ethandylbis(4-O-β-O-Galactopyranosyl-O-Gluconamide)

Production and purification similar to Example 5. From 3.40 g lactobionic acid-1,5-lactone and 0.44 g N,N'-dimethylethylene diamine are obtained 5.0 g of the compound of the title.

Melting point: IR (KBr): ^{1}H-NMR (D_2O):	125 - 133 °C ν = 2930, 1640, 1400, 1075 cm^{-1} δ 2,98, 3.16 (2S, 6H); 3,3 - 4,3 (m, 28H); 4,49 (d, 2H, 7Hz); 4,68 (H_2O, i. St.)

Example 17

N,N'-1,5-(1-Ethoxycarbonyl)-Pentandylbis(4-O-β-O-Galactopyranosyl-O-Gluconamide)

2.47 g lysinethylester-dihydrochloride are suspended in 40 ml amine-free dimethylformamide, they are transferred with 3.0 ml triethylamine and stirred for 15 minutes. Then are added 6.8 g lactobionic acid-1,5-lactone, heated to 60°C, and stirred for 1 day. It is filtered and the filtrate is stirred into 400 ml isopropanol. The precipitate is collected, dissolved in 60 ml dimethylformamide, and again precipitated with 300 ml isopropanol. The precipitation is repeated, it is washed with isopropanol and diethylether, and 4.05 g of the compound of a white powder are obtained.

Melting point: IR: ^{1}H-NMR (D_2O):	108 °C ν = 2930, 1735, 1655, 1650, 1075 cm^{-1} δ 1,25 (t, 3H, 7Hz); 1,2 - 2,2 (m, 6H); 3,25 (t, 2H, 5,5Hz); 3,4 -4,6 (m, 29H); 4,68 (H_2O, i. St.)

Example 18

Decasodium-N,N'-1,3-Propandylbis(2,3,4,5,6-Penta-O-Sulfo-O-Gluonamide

4.30 g N,N'-1,3-propandylbis-O-gluconamide are suspended in 30 ml dry dimethylformamide, are heated to 40°C, and are mixed under stirring with 23.8 g pyridine-sulfuric oxide complex. After a few minutes, the product precipitates in the form of the pyridineium salt as an oil. After 1 hour, it is allowed to cool off and the remaining solution is decanted. The oil is dissolved in 50 ml water and brought to a pH = 10 with [illegible] N sodium hydroxide. The solution is precipitated with water to 90 ml and introduced into 350 ml of a 1% sodium solution. The precipitate is washed with methanol and dried. 18.8 g of a colorless powder are obtained. The same is dissolved in 186 ml water. Into the solution are stirred 227 ml methanol. The precipitation is repeated until the compound of the title only is left. Decomposition starting at 190°C with a brown coloration.

IR (KBr):	ν = 2980, 1670, 1556, 1250, 1073, 1043, 1019, 770 cm^{-1}	
^{1}H-NMR (D_2O):	δ 1,87 (dt, 2H, 7Hz); 3,38 (dt, 4H, 7Hz); 3,8 - 4,8 (m, 4H); 4,8 - 5,4 (m, 8H); 4,88 (H_2O, i. St.)	
$[\alpha]_D^{20}$ = +28,2 (c = 5 in H_2O)		
Elementary Analysis:		
calculated:	N 22,10 %	S 1,93 %
found:	N 22,29 %	S 1,83 %
^{13}C-NMR (D_2O):	δ 29,87; 39,59; 69,08; 77,88; 78,10; 78,38; 78,85; 171,33; i. St.: CH_3OH δ 51,58	

Example 19

Decasodium-N,N'-1,12-Dodecandylbis(2,3,4,5,6-Penta-O-Sulfo-O-Gluonamide

6.80 g N,N'-1,12-dodecandylbis-O-gluconamide is transformed similar to Example 18 with 26.6 g pyridine sulfuric oxide complex and 20.5 g raw product are obtained. The pure product is obtained by gel chromatography of an aqueous solution in a Bephadax G 28 pillar. After freeze-drying is obtained a colorless powder, which decomposes with a brownish color between 175°C and 189°C.

IR (KBr):	ν = 2930, 2885, 1665, 1555, 1250, 1072, 1042, 1010 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,0 - 1,9 (m, 20H); 3,32 (m, 4H); 4,2 - 4,8 (m, 4H); 4,9 - 5,3 (m, 8H); 4,88 (H_2O, i.St.)
^{13}C-NMR (D_2O):	28,72; 30,52; 31,02; 42,30; 69,22; 77,87; 78,34; 78,85; 79,81; 171,09; i. St. CH_3OH δ51,58

Example 20

Hexadecasodium-N,N'-1,3-Propandylbis(2,3,5,6-Tetra-O-Sulfo-β-D-Gluonpyranosyl)-D-Gluconamide

79.1 g calcium lactobionate are dissolved in 240 ml water and the solution is treated with 240 ml Lewatit S 100 (H form). The ion exchanger is washed with 3 x 200 ml water and the unified dissolved product is narrow down as much as possible. The glass-like residue is dissolved in 700 ml amine-free dimethylformamide and is heated to boiling with 600 ml n-hexane in the water separator. After the water separation has been completed, the n-hexane is vaporized and the solution is transferred at room temperature with 7.7 g 1,3-diminopropane into 60 ml dimethylformamide. After 5 hours of stirring at 60°C, it is allowed to cool to approx. 30°C, it is diluted with 450 ml dimethylformamide and 400 g pyridine sulfuric oxide complex are added rapidly in stages under stirring. It is stirred for 1 hour between 40 and 45°C and is allowed to cool off. It is decanted from the excreted oil, the same is dissolved in 500 ml water, and the solution is placed with 30% sodium hydroxide to a pH = 10, it is completed with water up to a volume of 1.6 l, and the solution is stirred into 4.5 l of a 1% methanolic sodium acetate solution. The

precipitate is stirred with 1 l methanol, suctioned off, and dried. 250 g of a yellowish powder are obtained. The same is dissolved in 2 l water, transferred into 250 ml 30% hydrogen peroxide, and stirred for 1 hour at 45°C. After cooling, it is neutralized and completed with water up to 2.5 l. The solution is then stirred into 3.08 l methanol and is allowed to stand for 15 hours. It is decanted from the excreted oil and the same is rubbed with methanol. After drying are obtained 188.5 g colorless powder, the precipitation procedure is repeated four times and finally are obtained approx. 50 g of a pure compound of the title as a colorless powder, which color brownish starting at 172°C while decomposing and does not melt under 250°C.

IR (KBr): ^{1}H-NMR (D_2O): ^{13}C-NMR (D_2O):	ν = 2885, 1685, 1652, 1250, 1065, 1020, 927, 820 cm^{-1} δ 1,82 (t, 2H, 6,5Hz); 3,35 (t, 4H, 6,8Hz); 3,9 -4,4 (m, 8H); 4,4 - 4,8 (m, + H_2O-Signal bei 4,68 als i. St.); 4,8 - 5,4 (m, 10H) δ 30,31; 39,77; 68,36; 68,92; 74,22; 77,49; 77,78; 78,39; 78,78; 80,16; 103,55; 171,76; i. St.: CH_3OH 51,56	
$[\alpha]_D^{20}$ = + 13,3° (c = 5 in H_2O)		
Elementary Analysis:		
calculated: found:	N: 1.17 % N: 1.18 %	S: 21.48 % S: 21,61 %

Example 21

Pentadecasodium-Pentadeca-O-Sulfo-N,N'-1,3-Propandylbis(4-O-β-D--β-D-Gluonpyranosyl)-D-Galactopyranosyl-D-Gluconamide

3.77 g N,N'-1,3-propandylbis(4-O-β-O-galactopyranosyl-D-gluconamide) are dissolved in 60 ml dry dimethylformamide and mixed at 40°C under stirring by portions with 13.5 g pyridine sulfuric oxide complex. After 1 hour, it is processed like in Example 18 and one obtains 10.3 g yellowish sulfate-containing raw product. It is dissolved in 90 ml water, mixed with 10 ml 30% hydrogen peroxide, and stirred for 1 hour at 45°C. After cooling, 230 ml methanol are stirred in and it is allowed to stand for 15 hours. It is decanted from the excreted oil, the same is rubbed with methanol, and 6.72 g sulfate-free product (with a sulfur content of 20.6%). It is dissolved in 67 ml water, 62 ml methanol are stirred in, and it is allowed to stand for 18 hours. It is decanted from the excreted oil and into the residue are stirred 74 ml methanol. After 15 hours, the oil is isolated and the fractioned precipitation is repeated several times as above until the compound of the title is available pure. 0.53 g of a colorless powder are obtained, which decomposes starting at 180°C and takes on a brownish color.

IR (KBr):	ν = 2980, 1660, 1530, 1230, 1055, 1020, 930, 820 cm^{-1}		
^{1}H-NMR (D_2O):	δ 1,87 (t, 2H, 6Hz); 3,42 (t, 4H, 6Hz); 3,9 - 4,5 (m, 8H); 4,5 - 4,85 (m + H_2O-Signal bei 4,68 als L St.); 4,85 - 5,3 (m, 10H)		
^{13}C-NMR (D_2O):	δ 30,83; 39,79; 69,48; 69,11; 72,28; 74,38; 74,88; 77,43; 77,88; 78,14; 78,49; 79,03; 79,81; 79,84; 80,43; 103,43; 171,82; 172,81; L St.: CH_3OH51,58		
Elementaranalyse:	ber.:	N 1,23 %	S 21,04 %
	gef.:	N 1,21 %	S 20,91 %

Example 22

Hexadecamorpholium-N,N'-1,3-Propandylbis(2,3,5,8-Tetra-O-Sulfo-β-D-Galactopyranosyl)-D-Gluconamide

A solution of 1.78 g sodium salt of Example 20 is treated for 15 minutes with 18 ml Lewatit S 100 (H form), the ion exchanger is filtered away, and the filtrate is mixed with 1.03 g morpholin. After lyophilization are obtained 2.40 g yellowish powder.
Decomposition starting at 120°C and black coloration at 210°C.

IR (KBr):	ν = 2950, 2780, 1665, 1563, 1450, 1428, 1250, 1097, 1015, 925, 893, 858, 810 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,82 (dt, 2H; 6,5Hz); 3,15 (m, 8H); 3,35 (m, 4H); 3,80 (m, 8H); 4,0 - 4,4 (m, 8H); 4,4 - 4,8 (m, + H_2O-Signal bei 4,70 als L St.); 4,8 - 5,4 (m, 10H)

Example 23

Hexadecasodium-N,N'-1,6-Hexandylbis(2,3,5,6-Tetra-O-Sulfo-β-D-Galactopyranosyl)-O-Gluconamide

18.3 g N,N'-1,6-hexandylbis(4-O-β-D-galactopyranosyl-D-gluconamide) are mixed with 75.0 g pyridine sulfuric oxide complex similar to Example 18. After the first precipitation are obtained 58.9 g of a yellowish powder, which is purified as described in Example 20. One obtains finally approx. 15 g pure compound of the title in the form of a colorless powder that sinters at 120°C.
Decomposition starting at 170°C with brownish coloration.

IR (KBr):	ν = 2930, 2860, 1655, 1550, 1250, 1055, 1020, 928, 810 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,1 - 1,8 (m, 8H); 3,57 (m, 4H); 3,9 - 4,5 (m, 8H); 4,5 - 4,85 (m + H_2O-Signal bei 4,68 als t, St.); 4,85 - 5,3 (m, 10H)
^{13}C-NMR (D_2O):	δ 28,42; 30,74; 42,17; 68,58; 69,01; 74,39; 77,20; 77,80; 78,37; 78,94; 80,47; 103,21; 171,27 t, St. CH_3OH δ 51,58
$[\alpha]_D^{20}$ = + 9,9 (c = 5 in H_2O)	

Example 24

Hexadecasodium-N,N'-1,9-Nonandylbis(2,3,5,6-Tetra-O-Sulfo-β-D-Galactopyranosyl)-O-Gluconamide

Production and purification similar to Example 23. From 15.0 g N,N'-1,9-nonandylbis(4-O-β-D-galactopyranosyl-D-gluconamide and 83.0 g pyridine sulfuric oxide complex are obtained 45.0 g raw product. After purification: 10.5 g colorless powder.
Decomposition between 192-210°C with brown coloration.

IR (KBr):	ν = 2935, 2860, 1665, 1555, 1250, 1057, 1020, 925, 815 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,9 - 1,9 (m, 14H); 3,29 (t, 4H, 6,5Hz); 3,8 - 4,45 (m, 8H); 4,45 - 4,8 (m + H_2O-Signal bei 4,68 als t, St.); 4,8 - 5,4 (m, 10H)
^{13}C-NMR (D_2O):	δ 28,77; 30,83; 31,09; 31,32; 42,19; 68,68; 68,99; 74,46; 77,12; 77,78; 78,33; 78,93; 80,51; 103,11; 121,21 t, St.; CH_3OH, δ 51,58

Example 25

Hexadecasodium-N,N'-1,12-Dodecandylbis(2,3,5,6-Tetra-O-Sulfo-β-D-Galactopyranosyl)-D-Gluconamide

Production and purification similar to Example 23. From 4.23 g N,N'-1,12-dodecandylbis(4-O-β-D-galactopyranosyl-D-gluconamide and 19.1 g pyridine sulfuric oxide complex are obtained 13.30 g raw product. After purification: 3.6 g pure compound of the title as colorless powder. Decomposition between 188-198°C with brown coloration.

IR (KBr):	ν = 2940, 2880, 1685, 1555, 1250, 1055, 1020, 930, 820 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,9 - 1,9 (m, 20H); 3,35 (t, 4H, 6,5Hz); 3,8 - 4,6 (m, 8H); 4,5 - 4,8 (m, + H_2O-Signal bei 4,70 als l. St.); 4,8 - 5,4 (m, 10H)
^{13}C-NMR (D_2O):	δ 28,74; 30,50; 31,09; 31,44; 42,18; 68,78; 68,98; 74,50; 77,08; 77,80; 79,29; 78,94; 80,51; 103,07; 171,19 l. St.: CH_3OH δ 51,56

Example 26

Hexadecasodium-N,N'-1,12-Dodecandylbis(2,3,5,6-Tetra-O-Sulfo-β-D-Galactopyranosyl)-D-Gluconamide

From 0.34 g N,N'-1,12-dodecandylbis(4-O-β-D-galactopyranosyl-D-gluconamide) and 1.12 g pyridine sulfuric oxide complex are obtained, similar to Example 23, 0.68 g pure product. Decomposition starting at 169°C with brown coloration.

IR (KBr):	ν = 2930, 2855, 1670, 1560, 1250, 1070, 995, 935, 800 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,8 - 1,8 (m, 20H); 3,30 (m, 4H); 3,7 - 4,8 (m + H_2O-Signal bei 4,68 als l. St.); 4,8 - 5,3 (m, 10H)
^{13}C-NMR (D_2O):	δ 28,92; 30,95; 31,32; 31,84; 42,34; 69,20; 70,12; 75,57; 77,44; 77,57; 77,85; 79,33; 79,41; 79,97; 81,08; 102,53; 171,27 l. St.: CH_3OH δ 51,56

Example 27

Hexadecasodium-N,N'-1,12-Dodecandylbis(2,3,5,6-Tetra-O-Sulfo-4-O-(2,3,4,6-Tetra-O-Sulfo-α-D-Glucopyranosyl)-D-Gluconamide)

From 12.8 g N,N'-1,12-dodecandylbis(4-O-α-D-glucopyranosyl-D-gluconamide) and 64.8 g pyridine sulfuric oxide complex are obtained, similar to Example 23, 47.5 g raw product or 3.0 g pure product.
Decomposition from 175°C to 189°C with brown coloration.

IR (KBr):	ν = 2930, 2880, 1660, 1560, 1250, 1000, 943, 805 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,0 - 1,8 (m, 20H); 3,27 (m, 4H); 4,0 - 4,82 (m + Signal für H_2O bei 4,68 als l. St.); 4,82 - 5,25 (m, 10H); 5,52 (d, 2H, 3Hz)
^{13}C-NMR (D_2O):	28,84; 30,69; 31,15; 31,47; 42,41; 68,51; 69,29; 71,93; 78,14; 78,82; 77,91; 78,30; 78,44; 79,98; 80,93; 171,27

Example 28

Hexadecasodium-N,N'-1,12-Dodecandylbis(2,3,4,5-Tetra-O-Sulfo-6-O-(2,3,4,6-Tetra-O-Sulfo-α-D-Galactopyranosyl)-O-Gluconamide)

Similar to Example 23, from 3.30 g N,N'-1,12-dodecandylbis(6-O-α-D-galactopyranosyl-O-gluconamide) and 14.9 g pyridine sulfuric oxide complex are obtained 9.7 g raw product or 3.4 g pure product, which sinters starting at 87°C.
Decomposition starting at 182°C with brown coloration.

IR (KBr):	ν = 2930, 2855, 1660, 1565, 1260, 1080, 1027, 830 cm^{-1}
^{1}H-NMR (D_2O):	δ 1.0 - 1.9 (m, 20H); 3.25 (m, 4H); 3.9 - 4.4 (m, 8H); 4,4 - 4,8 (m + H_2O-Signal bei 4,68 als l. St.); 4,8 - 5.25 (m, 10H); 5,38 (d, 2H, 3Hz)
^{13}C-NMR (D_2O):	δ 28,72; 30,58; 31,03; 31,34; 42,30; 69,14; 69,77; 70,69; 74,51; 74,92; 77,91; 78,21; 78,49; 78,93; 80,75; 99,12; 171,28; l. St.: CH_3OH δ 51,58

Example 29

Hexadecasodium-N,N'-1,3-Propandylbis(2,3,4,5-Tetra-O-Sulfo-8-O-(2,3,4,6-Tetra-O-Sulfo-α-O-Galactopyranosyl)-D-Gluconamide)

From 0.34 g N,N'-1,3-propandylbis(6-O-α-D-galactopyranosyl-O-gluconamide) and 2.0 g pyridine sulfuric oxide complex are obtained, similar to Example 23, 0.96 g raw product or 0.50 g pure product.
Decomposition starting at 168°C with brown coloration.

IR (KBr):	ν = 1640, 1550, 1250, 1050, 1025, 830 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,89 (t, 2H, 6,5Hz); 3,35 (t, 4H, 6,5 Hz); 3,9 - 4,4 (m, 8H); 4,4 - 4,8 (m + H_2O-Signal bei 4,68 als l. St.); 4,8 - 5,25 (m, 10H); 5,38 (d, 2H, 3Hz)
^{13}C-NMR (D_2O):	δ 30,13; 39,84; 69,17; 69,86; 70,74; 74,53; 74,97; 78,00; 78,17; 78,37; 79,00; 80,81; 99,18; 171,70; l. St.: CH_3OH δ 51,57

Example 30

Hexadecasodium-N,N'-α,α'-m-Xylovlbis(2,3,5,6-Tetra-O-Sulfo-4-O-(2,3,4,6-Tetra-O-Sulfo-β-D-Galactopyranosyl)-D-Gluconamide)

From 12.0 g N,N'-α,α'-xyloylbis(4-O-β-D-galactopyranosyl-D-gluconamide) and 58.8 g pyridine sulfuric oxide complex are obtained, similar to Example 23, 28.0 g raw product or 5.3 g pure product.
Decomposition starting at 167°C with brown coloration.

IR (KBr):	ν = 2960, 1650, 1550, 1250, 1058, 1020, 830, 815 cm^{-1}
^{1}H-NMR (D_2O):	δ 3,8 - 4,85 (m + H_2O-Signal bei 4,68 als i. St.), 4,85 - 5,4 (m, 10H); 7,38 (s, 4H)
^{13}C-NMR (D_2O):	δ 45,51; 68,53; 69,15; 74,42; 77,24; 77,67; 77,91; 78,49; 79,08; 80,70; 103,29; 128,15; 128,88; 131,84; 140,80; 171,88; i. St. CH_3OH, δ 51,58

Example 31

Hexadecasodium-N,N'-4,4'-Dicyclohexylmethandylbis(2,3,5,6-Tetra-O-Sulfo-4-O-(2,3,4,6-Tetra-O-Sulfo-β-D-Galactopyranosyl)-D-Gluconamide)

Similar to Example 23, from 25.7 g N,N'-4,4'-dicyclohexylmethandylbis(4-O-β-D-galactopyranosyl-D-gluconamide) and 114.7 g pyridine sulfuric oxide complex are obtained 70.7 g raw product or 16.2 g pure product, which sinters starting at 120°C.
Decomposition starting at 160°C with brown coloration.

IR (KBr):	ν = 2930, 2960, 1660, 1650, 1250, 1055, 1020, 828, 815 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,6 - 2,4 (m, 20H); 3,65 (m, 2H); 3,8 - 4,5 (m, 8H) 4,6 - 4,85 (m + H_2O-Signal bei 4,68 als i. St.); 4,85 - 4,4 (m, 10H)
^{13}C-NMR (D_2O):	δ 30,18; 30,38; 30,75; 34,09; 44,40; 48,20; 49,45; 52,35; 68,27; 68,75; 74,35; 77,80; 78,41; 78,68; 79,48; 104,08; 170,81; i. St. CH_3OH δ 51,58
$[\alpha]_D^{20}$ = + 10,0 (c = 5 in H_2O)	

Example 32

Hexadecasodium-N,N'-1,6-(3,4-Dithiahexandylbis)(2,3,4,6-Tetra-O-Sulfo-β-D-Galactopyranosyl)-D-Gluconamide)

From 11.2 g N,N'-1,6-(3,4-dithiahexandylbis)4-O-β-D-galactopyranosyl-D-gluconamide and 53.4 g pyridine sulfuric oxide complex are obtained, similar to Example 23, 38.0 g raw product or 8.5 g pure product.
Decomposition starting at 183°C with brown coloration.

IR (KBr):	ν = 2965, 1665, 1650, 1250, 1065, 1015, 930, 810 cm^{-1}
^{1}H-NMR (D_2O):	δ 2,96 (t, 4H, 6,5Hz); 3,89 (m, 4H); 4,0 - 4,47 (m, 8H); 4,45 - 4,8 (m + H_2O-Signal bei 4,68 als l. St.); 4,8 - 5,3 (m, 10H)
^{13}C-NMR (D_2O):	δ 38,72; 41,06; 68,58; 69,05; 74,48; 77,40; 77,87; 78,48; 80,48; 103,48; 171,88; l. St. CH_2OH δ 61,58

Example 33

Hexadecasodium-N,N'-1,7-(4-Azaheptandylbis)(2,3,5,6-Tetra-O-Sulfo-4-O-(2,3,4,6-Tetra-O-Sulfo-β-O-Galactopyranosyl)-D-Gluconamide)

From 11.0 g N,N'-1,7-(4-azaheptandylbis)4-O-β-D-galactopyranosyl-D-gluconamide and 50.0 g pyridine sulfuric oxide complex are obtained, similar to Example 23, 16.4 g raw product or 2.2 g pure product.
Decomposition starting at 163°C with brown coloration.

IR (KBr):	ν = 2960, 2925, 2856, 1680, 1550, 1250, 1068, 1020, 927, 820 cm^{-1}
^{1}H-NMR (D_2O):	δ 2,98 (m, 2H); 3,17 (t, 4H, 7Hz); 3,44 (t, 4H, 8Hz); 3,9 - 4,4 (m, 8H); 4,4 - 4,85 (m + H_2O-Signal als l. Subel 4,68); 4,85 - 5,3 (m, 10H)
^{13}C-NMR (D_2O):	δ 28,11; 39,08; 48,12; 68,85; 69,24; 74,45; 76,94; 77,93; 78,46; 79,09; 80,71; 103,13; 172,06

Example 34

Hexadecasodium-N,N'-1,12-(4,9-Dioxadodecandylbis)(2,3,5,6-Tetra-O-Sulfo-4-O-(2,3,4,6-Tetra-O-Sulfo-β-O-Galactopyranosyl)-D-Gluconamide)

From 18.2 g N,N'-1,12-(4,8-dioxadodecandylbis)4-O-β-D-galactopyranosyl-D-gluconamide and 59.0 g pyridine sulfuric oxide complex are obtained, similar to Example 23, 37.1 g raw product or 9.3 g pure product, which sinters starting at 120°C.
Decomposition starting at 170°C with brown coloration.

IR (KBr):	ν = 2960, 2880, 1665, 1555, 1250, 1085, 1022, 928, 815 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,84 (m, 4H); 1,88 (t, 4H, 6,8Hz); 3,0 - 3,9 (m, 12H); 3,9 - 4,45 (m, 8H); 4,45 - 4,8 (m + H_2O-Signal bei 4,68 als l. St.); 4,8 - 5,3 (m, 10H)
^{13}C-NMR (D_2O):	δ 27,82; 30,78; 39,02; 68,84; 69,01; 70,54; 72,96; 74,44; 77,02; 77,79; 78,33; 78,94; 80,52; 103,10; 171,48; i. St.: CH_3OH δ 51,58
$[\alpha]_D^{20}$ = + 9,0 (c = 5 in H_2O)	

Example 35

Hexadecasodium-N,N'-Dimethyl-N,N'-1,2-Ethandylbis(2,3,5,6-Tetra-O-Sulfo-4-O-(2,3,4,6-Tetra-O-Sulfo-β-O-Galactopyranosyl)-D-Gluconamide)

From 2.50 g N,N'-dimethyl-N,N'-1,2-ethandylbis(4-O-β-D-galactopyranosyl-D-gluconamide) and 12.4 g pyridine sulfuric oxide complex are obtained, similar to Example 23, 8.2 g raw product or 1.2 g pure product.
Decomposition from 188-200°C with brown coloration.

IR (KBr):	ν = 2870, 1660, 1250, 1015, 930, 815 cm^{-1}
^{1}H-NMR (D_2O):	δ 3,0 - 4,0 (m mit s bei 3,38; 10H); 4,6 - 4,7 (m, 14H); 4,70 (H_2O, l. St.); 4,9 - 5,4 (m, 10H); 5,54 (d, 2H, 4Hz)
^{13}C-NMR (D_2O):	δ 38,96; 48,28; 68,36; 69,23; 74,17; 75,11; 77,29; 77,73; 78,00; 78,46; 78,78; 79,80; 103,35; 171,25; i. St.: CH_3OH, δ 51,58

Example 36

Hexadecasodium-N,N'-Dimethyl-1,5-(1-Ethoxycarbonyl)-Pentandylbis(2,3,5,6-Tetra-O-Sulfo-4-O-(2,3,4,6-Tetra-O-Sulfo-β-D-Galactopyranosyl)-D-Gluconamide)

From 3.6 g N,N'-1,5-(1-ethoxycarbonyl)-pentandylbis(4-O-β-O-galactopyranosyl-D-gluconamide) and 15.8 g pyridine sulfuric oxide complex are obtained, similar to Example 23, 8.7 g raw product or 1.2 g pure product, which sinters at 60°C.
Decomposition starting at 181°C with brown coloration.

IR (KBr):	ν = 1730, 1650, 1550, 1250, 1055, 1020, 830, 810 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,0 - 2,2 (m, 8H, mit t bei 1,31, 7 Hz); 3,30 (m, 2H); 3,9 - 4,8 (m mit H_2O-Signal bei 4,68 als l. St.); 4,8 - 5,3 (m, 10H)
^{13}C-NMR (D_2O):	δ 15,94; 28,68; 30,54; 33,17; 41,87; 68,93; 65,19; 68,23; 68,53; 69,04; 74,36; 77,33; 79,81; 78,45; 78,80; 79,81; 80,47; 103,38; 103,89; 171,39; 171,85; 176,12

Example 37

N,N'-1,3-Propandylbis-D-Gluconamide

3.58 g D-gulono-γ-lactone and 0.84 ml 1,3-diaminopropane are dissolved in 40 ml dimethylformamide and stirred for 6 hours at 80°C. Then the mixture is stirred into 200 ml isopropanol and the precipitate is washed with isopropanol and diethylether. The solids are dissolved in 20 ml dimethylformamide and is again precipitated with 200 ml isopropanol. The precipitate is dissolved in water and are freeze-dried. One obtains 2.2 g of a colorless powder.

Melting point: ^{1}H-NMR (D_2O): ^{13}C-NMR (D_2O):	ν = 2930, 2880, 1645, 1545, 1440, 1080 cm^{-1} δ 1.74 (dt, 2H, 8,5Hz); 3.27 (t, 4H, 6,5Hz); 3,45 - 4.05 (m, 10H); 4.23 (d, 2H, 8Hz); 4.88 (H_2O, l. St.) δ 30.65; 39.02; 65.13; 72.64; 74.89; 75.00; 75.12; 178.78; l. St. CH_2OH δ 61.56

Example 38

N,N'-1,2-Propandylbis-D-Galactonamide

Similar to Example 37, one obtains from 7.12 g D-galactono-γ-lactone and 1.48 g 1,2-diaminopropane, 4.1 g of the compound of the title as a colorless powder.

Melting point: IR (KBr): ^{1}H-NMR (D_2O): ^{13}C-NMR (D_2O):	183-193°C under decomposition and brown coloration ν = 2940, 1656, 1552, 1109, 1055, 1044, 1028, 865 cm^{-1} δ 1;18 (d, 3H, 6Hz); 3,1 - 4,8 (m, 15H); 4,88 (H_2O, l. St.) δ 19.64; 19.77; 48.16; 47.87; 48.10; 68.90; 71.93; 72.64; 73.49; 177.75; 178.42; 178.54

Example 39

N,N'-1,4-Butandylbis-L-Mannonamide

Similar to Example 18, one obtains from 3.68 g L-mannono-γ-lactone and 0.90 g futresin, 2.4 g of the compound of the title as a colorless powder.
Decomposition from 181-188°C with brown coloration.

IR (KBr):	ν = 2955, 2925, 2855, 1643, 1555, 1231, 1088, 1043, 1031, 880, 740, 640 cm^{-1}
^{1}H-NMR (D_2O):	δ 1.58 (m, 4H); 3.30 (m, 4H); 3.75 (m, 8H) 4.02 (d, 2H, 7Hz); 4.28 (d, 2H, 7Hz); 4.88 (H_2O l. St.)
^{13}C-NMR (D_2O):	δ 28.42; 41.38; 65.67; 72.58; 72.78; 73.43; 75.19 ; 177.09;

Example 40

N,N'-Dilactobionylhydrazine

Similar to Example 37, one obtains from 9.6 g lactobionic acid-1,6-lactone and 0.5 ml hydrazine hydrate, 8.1 g raw product. Pillar chromatography via Fractogel TSK HW 40S delivers the pure product as a colorless powder after freeze-drying.

Example 41

Decasodium N,N'-1,3-Propandylbis(2,3,4,5,6-Penta-O-Sulfo-D-Gulonamide)

Similar to Example 18, from 2.2 g N,N'-1,3-propandylbis-O-gulonamide and 12.3 g pyridine sulfuric oxide complex are obtained 9.8 g raw product or 6.4 g pure product as a colorless powder. Decomposition starting at 165°C with brown coloration.

IR (KBr):	ν = 2960, 1675, 1555, 1250, 1070, 1010, 925, 805 cm^{-1}
^{1}H-NMR (D_2O):	δ 1.85 (m, 2H); 3.34 (m, 4H); 4.52 (d, 4H, 3,5Hz); 5.07 (m, 6H); 5.34 (d, 2H, 3,5 Hz); 4.68 (H_2O, l. St.)
^{13}C-NMR (D_2O):	δ 30.05; 39.52; 68.78; 76.28; 78.41; 77.78; 80.14; 171.15; l. St. CH_3OH δ 51.59

Example 42

Decasodium N,N'-1,2-Propandylbis(2,3,4,5,6-Penta-O-Sulfo-D-Galactonamide)

Similar to Example 18, from 3.3 g N,N'-1,2-propandylbis-O-galactonamide and 19.5 g pyridine sulfuric oxide complex are obtained 13.0 g raw product or 9.8 g pure product as a colorless powder. Decomposition starting at 191°C with brown coloration.

IR (KBr):	ν = 2970, 1665, 1550, 1250, 1065, 1040, 1007, 900 cm^{-1}
^{1}H-NMR (D_2O):	δ 1.28 (d, 3H, 6,5Hz); 2.9 - 4.3 (m, 3H); 4.3 - 4.6 (m, 4H); 4.66 (H_2O, l. St.); 4.8 - 5.3 (m, 6H)
^{13}C-NMR (D_2O):	δ 19.20; 45.94; 46.15; 67.81; 69.07; 78.42; 78.66; 78.90; 170.84; 171.03; 191.53 l. St. CH_3OH δ 51.57

Example 43

Decasodium N,N'-1,4-Butandylbis(2,3,4,5,6-Penta-O-Sulfo-L-Mannonamide)

Similar to Example 18, from 2.6 g N,N'-1,4-butandylbis-L-mannonamide and 14.1 g pyridine sulfuric oxide complex are obtained 10.5 g raw product or 7.2 g pure product as a colorless powder. Decomposition starting at 180°C with brown coloration.

IR (KBr):	ν = 2980, 2930, 2850, 1670, 1555, 1250, 1075, 1010, 825 cm^{-1}
^1H-NMR (D_2O):	δ 1.85 (m, 4H); 3.31 (m, 4H); 4.43 (m, 4H); 4.8-5.03 (m, 4H); 5.15 (m, 4H); 4.68 (H_2O, i. St.)
^{13}C-NMR (D_2O):	δ 27.98; 41.82; 68.15; 78.81; 79.36; 79.75; 170.93; i. St. CH_3OH δ 51.55

Example 44

Hexadecasodium N,N'-bis(2,3,6,8-Tetra-O-Sulfo-4-O-(2,3,4,6-Tetra-O-Sulfo-β-D-Galactopyranosyl)-Glucoovl)-Hydrazine

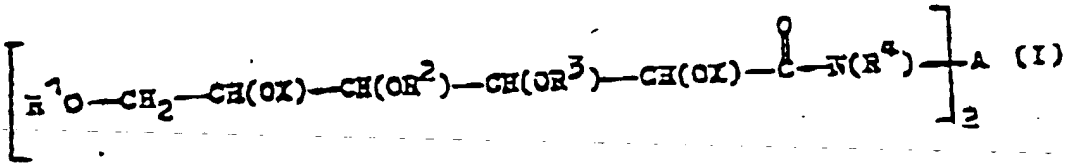
Similar to Example 18, one obtains from 6.0 g N,N'-dilactobionyl hydrazine and 33.7 g pyridine sulfuric oxide complex, 17.5 raw product or 7.3 g pure product.

Example 45

At room temperature are dissolved 5,000 Kg dry substance of hexadecasodium N,N'-1,3-propandylbis(2,3,5,6-tetra-O-sulfo-4-O(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-O-gluconamide) under constant stirring in 40 ml aqua ad inlectabilia. After setting the pH value of the solution to 7.5 with diluted sodium hydroxide, one completes with aqua ad inlectabilia up to 50.00 l and filters through a membrane filter with a pore width of 0.2 µm. The solution is filtered under aseptic conditions into ampules of 1 ml and the same are melted.

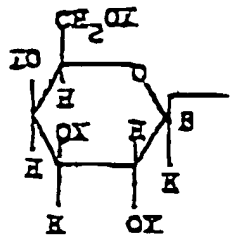
Claims

1. Polysulfuric acid esters of bis-aldonic acid amides and their derivates of general formula I,

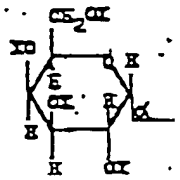


(I)

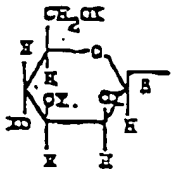
wherein either
all the residues R^1, R^2, and R^3 stand for X independently from each other, or
two of the residues R^1, R^2, and R^3 stand for X and the third stands for a residue of formulas II-VII.



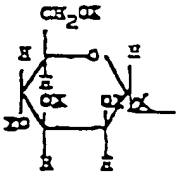
(II)



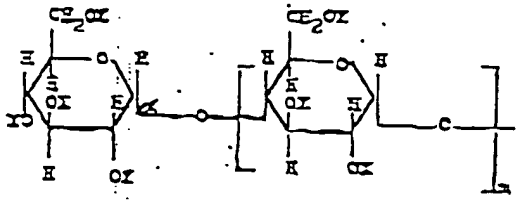
(III)



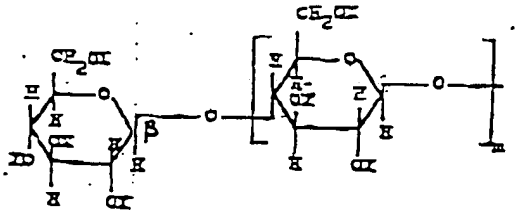
(IV)



(V)



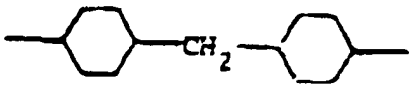
(VI)



(VII)

X means in the formulas I to VII simultaneously or independently from each other mean a hydrogen atom or the group $-SO_2H$, wherein at least one X stands for the group $-SO_2H$,
m stands for 0, 1, 2, 3, 4, 5, or 6,
A in formula I stands for an, if necessary, substituted with one or several residues $-CO_2R^5$, straight-chain or branched, saturated alkyl residues with 2 to 22 carbon atoms, and this alkylene residue, if necessary, is interrupted by up to 5 -O-, -S-, -S-S-, $-S(O)_{[illeg.]}$

$-\overset{O}{\overset{\|}{C}}-NH-$ or/and $-NR^2$ groups of cycloalkylene or arylene residues, or A stands for a simple bond or the residue



n is 1 or 2,
R^4, R^5, and R^6 simultaneously or independently of each other mean a hydrogen atom or a C_1-=C_{26} alkyl residue,
as well as their salts with inorganic or organic bases.

2. Compounds according to claim 1, characterized in that each X in the formulas I to VII stand for the group $-SO_3H$.

3. Compounds according to claim 1, characterized in that in the formulas I to VII at least half of the available X groups represent a $-SO_3H$ group.

4. Compounds according to claim 1, characterized in that R^2 and R^1 stand for X.

5. Compounds according to claim 4, characterized in that R^1 means the residue III or the residue VI with m = 0.

6. Compounds according to claim 1, characterized in that R^1 and R^3 stand for X.

7. Compounds according to claim 1, characterized in that R^2 means the residue II and the residue VI with m = 0 or the residue VII with m = 0.

8. Compounds according to one of claims 4 to 7, characterized in that A in formula I means a polymethylene residue $-(CH_2)_\rho$, with ρ = 2 to 12.

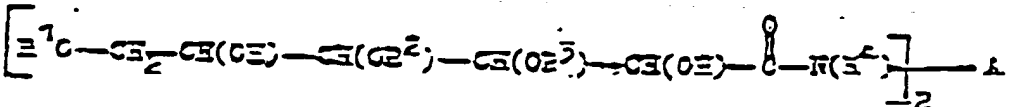
9. Compounds according to one of claims 4 to 7, characterized in that A in the formula I means a polymethylene residue $-(CH_2)_\rho$, with ρ = 2 to 12.

10. Compounds according to one of claims 4 to 7, characterized in that A in the formula I represents a straight-chain alkylene residue with 2 to 22 carbon atoms, whose chain is interrupted by the groups -O, -S-, -S,S-, $-S(O)_n$-,

$-\overset{O}{\overset{\|}{C}}-NH-$ and/or $-NR^6$, wherein n and R^6 have the meanings mentioned in claim 1.

11. Compounds according to one of claims 8 to 10, characterized in that A in the formula I is substituted by one, two, or three residues $-CO_2R^5$, wherein R^5 has the meaning mentioned in claim 1.

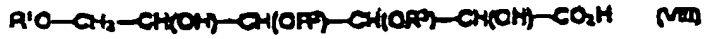
12. Process for producing polysulfuric acid esters of bis-aldonic acid amides and their derivates of formula I according to claim 1, characterized in that bis-aldonic acid amides of general formula IX,



(IX)

wherein R^1, R^2, R^3, R^4, and A are the meanings mentioned in claim 1, wherein however X in the formulas II to VII stands for hydrogen mixed in an aprotic solvent with a sulfatizing agent and the products obtained in this way are transferred with an inorganic or organic base into the corresponding salts.

13. Process according to claim 12, characterized in that, without isolation of the intermediate stages, aldonic acids of general formula VIII,



wherein R^1, R^2, and R^3 have the meanings mentioned in claim 1, wherein however X in the formulas II to VII stands for a hydrogen atom, in which bis-aldonic acid amides of general formula IX are transferred and transformed into their polysulfuric acid esters.

14. Pharmaceutical containing one or several compounds of general formula I, according to one of claims 1 to 11, together with the usual carrier and auxiliary substances.